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Vitamin D deficiency and its immunological and genetic determinants in middle eastern populations: Emphasis on Iraqi data

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Abstract

Among the most common, yet underestimated nutritional deficiencies in the world is vitamin D deficiency (VDD), that remains especially pronounced among MENA populations including Iraq. Noting the considerable solar radiation in the region, epidemiological surveys indicate a deficiency level of 50-90% among adults - a paradox explained by the concurrence of cultural clothing habits and indoor lifestyle, few dietary sources and now increasing genetic factors. We provide here a narrative review of the epidemiology of VDD in MENA, with particular emphasis on Iraqi governorates-containing novel data from Baghdad, Basrah, Sulaymaniyah, and Kirkuk-and attempt an integrative analysis of both the immuno-biological consequences and genetic architecture of VDD in these populations. The vitamin D receptor (VDR) is expressed on nearly all immune cells and mediates pleiotropic effects on innate and adaptive immunity, connecting hypovitaminosis D with enhanced inflammatory tone, decreased antimicrobial peptide production, and altered T-cell homeostasis. Here we present genome-wide association studies (GWAS) performed in Middle Easterners from the Qatar Biobank, identifying instrumented genetic variation at the GC, CYP2R1 and VDR loci that explain ~18% of vitamin D heritability with a different variant architecture than common across European populations. Compared to Iraq where no similar genomic data exists, this represents the most significant barrier to bridging genetic insight to local public health policy. At the end of this review, we have presented prioritised recommendations for integrated genomic-environmental research, validation of major cut-off values in Iraq, targeting supplementation programmes and food fortification strategies.

Keywords: **V**itamin D deficiency; Iraq; Middle East; MENA; immunomodulation; VDR; GC; GWAS; Kirkuk; Basrah; Sulaymaniyah

1. Introduction

Introduction Vitamin D deficiency has emerged as a very common and neglected public health problem in the Middle East- North Africa (MENA) region where several interrelated environmental, cultural, and biological risk factors overlap to significantly affect the vitamin D status of populations. Historically, vitamin D deficiency has been defined clinically by a serum 25-hydroxyvitamin D [25(OH)D] [targeted for debate] concentration lower than 20 ng/mL (<50 nmol/L), however insufficiency is most commonly defined as a serum level between 20 and 30 ng/mL. However, these universally accepted thresholds are still being both debated and discussed within each regional scientific societies because locally derived cut-off values might correlate more accurately to the actual physiological inflection points and health association relevant to Middle Eastern and Iraqi populations (Alabbood & Alrubaye, 2026). On a global scale, Cui et al. Most importantly, a large pooled analysis with 7.9 million individuals from 308 studies in 81 countries found that nearly half (47.9%) of the global population has a serum 25(OH)D level less than the sufficient cut-off point of <50nmol/L (Wang et al., 2023).

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A suboptimal physiological vitamin D level has been identified as the sole and most prevalent deficiency across the entire Eastern Mediterranean Region, with an impressive and alarming prevalence of 71.8%. It is the very nature of this statistic, being derived directly from and explicitly calculated based on raw sample data collected from the specific population under study that best illustrates the true severity of this disease. This compelling data helps underscore a potentially serious and widespread public health challenge that extends well beyond this regional context, to then raise an important global concern.

Investigations are warranted to resolve the bio-chemical and clinical conundrum of extremely high prevalence of vitamin D deficiency in Makkah estarinde not limited to its location but suggest a global problem across Asia in association with unknon factor/overt mechanism. The social and behavioral biology of this epidemiological paradox is complicated. Although the environment is replete with sunshine, actual naked skin exposure is much limited due to conservative dressing and contemporary indoor sedentary habits. Moreover, these populations have reduced cutaneous vitamin D synthesis as a consequence of higher natural melanin levels and traditional local diets do not provide enough natural or fortified sources of the nutrient. Worse still, there are numerous single population specific genetic mutations that influence vitamin D metabolism and cellular receptor expression making addressing this deficiency so widely spread extremely challenging (Hendi et al., 2023; Rahman et al., 2023).

Results of a well-designed, multicenter, population-based cohort study involving 5,014 subjects from Iraq found that the overall prevalence of vitamin D deficiency (defined as serum 25(OH)D level <20 ng/mL) was nearly 39% in this sample. Notably, compared to the central and southern regions, the mean serum 25(OH)D concentrations in areas geographically proximate to Kirkuk, located in northern Iraq were lower (21.7 ± 17 ng/mL) with significant regional differences within vitamin D status (Mahmood et al., 2025). In addition, more specific studies in Baghdad demonstrated higher rates of deficiency (84% of male's vs 89.33 females); a further thorough survey was conducted, showing high frequency of Both severe vitamin D insufficiency and deficiency among females and males (Khisho & Alfahad, 2025).

Recently, the newly available prevalence data from Kirkuk governorate in northern Iraq, including relevant variations with regard to ethnic backgrounds and climatic conditions has added a valuable addition to this expanding architecture. A study in 2025 at Azadi Teaching Hospital (using blood from 388 orthopedic out-patients) showed a vitamin D deficiency prevalence of 62.1% with an additional 19.9%, classed as vitamin D insufficient. In this study, statistical significance was also associated with vitamin D deficiency and some other demographics and clinical parameters including female sex, obesity and having chronic disease comorbidities, indicating vulnerable subpopulations of our region (Rashid et al., 2025).

Background: Despite vitamin D deficiency (VDD) being imperatively prevalent in Iraq, the immunological impact and genetic contributing factors are not extensively studied. In another study from Erbil, 289 patients ASD funded with VDD has been reported in 51.9% of cases and moderate deficiency to be 27.6% [28]. The prevalence of VDD was higher in females compared to males (55.5% vs. 49.4%; p =0.021) and associated with diabetes, obesity, co-morbid heart disease and COVID-19 (Ameen et al., 2023). Surveying 1143 individuals in Duhok revealed a total deficiency prevalence of 44.9%, the highest being among the age group 20-40 (46.23%). Higher deficiency rates in females (43.03% vs 37.8%) compared to males were observed once again, highlighting the persistent gender differences in vitamin D status (Mohammed et al., 2021).

NGS and GWAS for Vitamin D levels R1: Regionally, NGS of more than 6,000 Qatar Biobank participants are defining the Middle Eastern genome-wide genetics of vitamin D levels. Through a genome-wide association study, new genetic variants at the GC locus and chromosome 11 were also identified (Hendi et al., 2023), with vitamin D heritability being ~18%. Although non-published GWAS have yet to be conducted in Iraq, addressing this gap is crucial for informing tailored public health responses as well as advancing genomic knowledge in the region.

Objectives: This comprehensive review aims to:

Summaries the epidemiology of vitamin D deficiency (VDD) for various Middle East and North Africa (MENA) populations with a pointed focus on political, ecological, demographical ideas from Iraq and more specifically, Kirkuk Governorate.

Describe possible immune molecular mechanisms coupled with effects associated with vitamin D.

Critique evidence relating to VDD or its linking immunity in clinical studies conducted on MENA populations.

Provide the underlying rationale for genetic predisposition which may make certain individuals more likely than others to develop VDD in this region while highlighting knowledge gaps that need better Iraqi or even MENA-centric genomic investigations.

2. Vitamin D Biology and Immune Function

Knowledge of the biological pathways associated with vitamin D should assist in assimilating data from age-varied clinical cohort and Middle Eastern quantitative trait loci (QTL) datasets. Vitamin D is a pro-hormone and needs two rounds of hydroxylation to activate. PV exposure induces the conversion in skin of 7-dehydrocholesterol to cholecalciferol (vitamin D3) first under the influence of UVB. This is converted to 25(OH)D, the main bioactive form and universal indicator of vitamin D status by CYP2R1 in the liver. The final step of activation happens in the kidney, where CYP27B1 converts 25(OH)D to the active hormone [2]1,25$(OH)_2$D (calcitriol). Extrarenal tissues such as immune cells and the placenta also generate calcitriol in situ via CYP27B1 for the purpose of sustaining immune homeostasis. Lastly, CYP24A1 catabolizes both 25(OH)D and 1,25$(OH)_2$D for safety concerns to limit toxicity and control calcitriol bioavailability (Voltan et al., 2023).

2.1. The Vitamin D Receptor and Gene Regulation

The vitamin D receptor (VDR) is a nuclear hormone receptor encoded on chromosome 12q which heterodimerizes with the retinoid X receptor (RXR). After binding its active ligand calcitriol, VDR heterodimerizes with RXR. Then this versatile complex penetrates into the nucleus and attaches to VDREs, responsible for regulating dozens of genes related with calcium homeostasis, cellular differentiation, immunity, or apoptosis (Alswailmi et al., 2021). Since VDR is expressed by most immune cells, calcitriol is an essential modulator of both innate and adaptive immune function.

Polymorphisms in the VDR gene (such as FokI, TaqI, BsmI and ApaI) result in alterations of the receptor expression levels and also binding affinity or transcriptional activity, which produce marked inter-individual variability to calcitriol response (Voltan et al.). Resistance story to vitamin D is the attenuated cellular response, in spite of sufficient circulating 25-hydroxyvitamin D. The silenced response results from decreased VDR expression, dysfunctional signaling pathways, or a specific VDR haplotype that then leads to impaired vitamin D physiology.

2.2. Innate Immune Effects

Innate immunity is modulated by vitamin D via regulation of antimicrobial peptides (AMPs). Upon stimulation of host defenses by pathogen-associated molecular patterns (PAMPs), the vitamin D receptor (VDR) and CYP27B1 enzyme are upregulated in TLR2/1-activated innate immune cells. This allows the production of calcitriol (active vitamin D) locally, which acts via autocrine and paracrine signaling to induce AMPs, including cathelicidin (CAMP) and β-defensin 2 (DEFB4). These molecules are potent death agents either by killing pathogens through the direct disruption of microbial cell membranes or by carrying out indispensable immunomodulatory functions (Alswailmi et al., 2021; Cutolo, 2023).

TLR activation induces endogenous calcitriol synthesis in macrophages and dendritic cells. These establish an autocrine loop that amplifies cathelicidin production and enhances innate immunity towards pathogens (Cutolo 2023). Moreover, 1,25$(OH)_2D_3$ promotes macrophage chemotaxis and phagocytosis. It triggers the generation of antibacterial reactive oxygen species (ROS), and stimulates autophagy for the degradation of intracellular pathogens such as mycobacteria (Ghaseminejad-Raeini et al., 2023).

Vitamin D also augments general immunity as observed by the expression of VDR in time-course studies performed on innate immune cells (including monocytes, macrophages, neutrophils, natural killer cells and dendritic cells) rendering them sensitive to vitamin D and stimulating broad-spectrum immunity (Ghaseminejad-Raeini et al., 2023). Moreover, vitamin D controls the homeostasis of iron during infection by downregulating hepcidin (HAMP) expression to restrain microbial growth. Combined with transforming growth factor-beta it also enhances leukotriene synthesis. At the same time, calcitriol preserves immune homeostasis and limits the risk of tissue damage to regulate TLR recognition of PAMPs in order to protect the host from damage due to excessive inflammation triggered by immune hyperactivation (Alswailmi et al., 2021).

2.3. Adaptive Immune Effects

In adaptive immunity, VDR and CYP27B1 co-express in activated T and B lymphocytes along with their activation. Calcitriol (the active form of vitamin D3) is able to inhibit pro-inflammatory Th1 cells and their secreted cytokines (IFN-γ, TNF-α). That inhibits Th17 differentiation via reducing IL-17 production. In activated T cells from males and females, experiments show that calcitriol reduces IL-17, IFN-γ, and TNF-α. Unlike males, females also exhibited enhanced

secretion of the anti-inflammatory cytokine IL-10. This switch to the anti-inflammatory state in these cells is accounted for by VDR overexpression (Peruzzu et al., 2022). Calcitriol induces a tolerogenic profile through the STAT6-GATA3 pathway and reprograms immunity from Th1 to Th2 and Treg phenotypes. In support of this, a trial investigating five years of vitamin D supplementation observed a 22% reduction in autoimmune disease incidence (Cutolo, 2023). Calcitriol also contributes to improved expression of Foxp3 in Tregs (through VDR activation) and favoring immature dendritic cell induction (Ghaseminejad-Raeini et al., 2023). Calcitriol inhibits immunoglobulin synthesis and plasma cell differentiation in B lymphocytes, which broadly suppresses humoral immunity (Alswailmi et al., 2021). So, the calcitriol and VDR interaction leads to an extensive systemic epigenetic reprogramming of the immune system going from a proinflammatory setting to a homeostatic tolerogenic phenotype.

Such immunoregulatory role is especially relevant given the high prevalence of autoimmune and cardiometabolic disorders in populations from the Middle East.

2.4. Vitamin D and Nutrigenomics

Vitamin D stands as a quintessential and paradigmatic component in the rapidly progressing and multifaceted field of nutrigenomics. As beautifully stated by Carlberg (2023), vitamin D and its various metabolites are among the most illustrative nutritional epigenomics examples, mainly because 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$] has profound and direct control on many aspects of genomic architecture through the vitamin D receptor (VDR). These effects include the modulation of chromatin accessibility, dynamic changes in histone post-translational modifications, transcription factor binding (enhancement or inhibition), and complex three-dimensional chromatin conformation reorganization in multiple tissues and cell types. But importantly, human intervention studies have revealed important and clinically relevant pharmacogenomic variability in the molecular and transcriptomic response to vitamin D_3 supplementation about one-fourth of subjects are classified as low responders with respect to target gene regulation, requiring far higher doses of supplementation to provoke equivalent transcription responses that occur at lower dosage levels in mid- or high-responder individuals (Carlberg, 2023).

3. Vitamin D Deficiency in the Middle East

Tertiary care centers B. Epidemiological evidence C. Vitamin D deficiency NARI Abstract: The vulnerably older populations in the [Middle Eastern (ME)] countries, as witnessed by clinicians throughout many years of experience on grounds and clinics have reported some of the highest global prevalence's of vitamin D Few efforts attainable Rasht Chy et al. Pooled analysis performed by Cui et al. In a comprehensive analysis, published in (2023), which included 7.9 million participants from 308 individual studies across 81 countries, the authors concluded that all WHO regions had vitamin D deficiency but identified our region, Eastern Mediterranean Region as having the highest burden of this problem. In particular, they observed that 35.2% (95% confidence interval: 29.6-41.0%) individuals had serum 25-hydroxyvitamin D [25(OH)D] concentrations <30 nmol/L in this region and an alarming 71.8% <50 nmol/L; To help put this global perspective into context, a meta-analysis additionally focused just on the MENA region reported by Machuron et al. This most recent meta-analysis, combined from 41 studies involving a total of 594,712 subjects in this area generated a mean serum concentration for 25(OH)D which nevertheless remained worryingly low at only 46 nmol/L (mean concentration below the optimal sufficiency range in the body up to ≥50 nmol/L). While the overall difference of 6 nmol/L in vitamin D status is considered small, Machuron et al. (2025) reported that this gender gap was even more pronounced in some countries with an especially large difference of 18 nmol/L being observed in Pakistan, and gaps wider than those obtained for the total population for Turkey (10 nmol/L), and Bahrain (12 nmoL/L).

3.1. Prevalence Patterns

Country-based epidemiological surveys across the Gulf Cooperation Council (GCC) countries and parts of the Levant region have reported equally disturbing and unacceptably prevalent high levels of vitamin D deficiency (VDD). By way of example, a 2023 published cross-sectional study including a very large size of the conducted sample (n=12,346) of UAE citizens showed that as many as 72% were affected by VDD. In a similar fashion, as a very large population-based survey of 102,342 adults conducted in Qatar reported almost the same deficiency proportion: 71.4% (Faraj et al., 2024). Across Saudi Arabia, the magnitude of vitamin D deficiency has been found to be highly variable (estimates range from ~37% over 80%) and is highly dependent on the subpopulation studied and diagnostic threshold criterion used; describing typically congenital high (i.e., dietary or intrinsically low) rates within reproductive age women and elderly groups, but none in men (<40 years) time higher than control countries like Korea (Cui et al., 2023).

3.2. Key Risk Factors

VDD in the Middle East has occasional, significant modifiable and structural risk factors playing an important role not just behavioural, but more importantly environmental (environmental theory) in the relation of Vitamin D status among other socio-demographic variables within the region population. One of the most prominent behavioural factors constitutes conservative clothing practices that mostly include wearing full-body covering attires and coupled with a variety of head cover. These clothing practices greatly reduce the skin's direct exposure to sunlight, specifically ultraviolet B (UVB) radiation, and play a significant role in accounting for most of the difference in serum vitamin D levels that are usually found in women compared to men who live in this region (Machuron et al., 2025; Cui et al., 2023). Apart from deficits in apparel, and a sedentary indoor occupational and recreational lifestyle further drive avoidance of sun exposure, the phenomenon also observed in congested mega-cities within the Gulf region characterized by viciously hot dry summer temperatures that discourage daylight outdoor living.

3.3. Public Awareness and Behavior

The state of regional vitamin D nutrition literacy is very low. This was highlighted in an assessment of the Sulaymaniyah Governorate, a region in Iraq's Kurdistan region which found that 90.9% knew they were vitamin D deficient but only just more than 30% knew how much sun exposure was enough to meet their needs. (Mohammed. salih et al., 2023).

4. Focus on Iraq: Prevalence, Cut-Offs, and Clinical Correlates

Repeatedly In Iraq, large cross-sectional studies have confirmed that low levels of vitamin D are widely and alarmingly present in apparently healthy adult populations, generating persistent and sometimes heated discussions on establishing region-specific cut-off points for this nutrient. The epidemiology of vitamin D status in the country is characterized by marked geographical heterogeneity and also by intense methodological heterogeneity in the determination and interpretation of thresholds used to assess deficiency. Moreover, an increasing clinical literature has clearly identified dysfunctional vitamin D pathways as mediators of a range of adverse skeletal and chronic metabolic effects conditions that underscore the need for measurement and correction of vitamin D in this context.

4.1. Prevalence Across Iraqi Governorates

In study of 300 adults from Baghdad showing rates as much as 84% in males and 89-33% in females for Vitamin D Deficiency (VDD). In a national study of 5,014 subjects, the overall VDD prevalence (≤20 ng/mL) was shown to be 39%. The average (21.7 ± 17 ng/mL) was the lowest in Northern Iraq and progressively increased, with averages for the middle region (24.8 ± 14.3 ng/mL) and southern Iran (25.1 ± 14.2 ng/mL). Furthermore, they found the winter vit. D concentrations were significantly lower in comparison to autumn (Mahmood et al., 2025).

In a survey of Sulaymaniyah, Iraq in 2022, virtually VDD was considerably greater amongst girls than males (Mohammed Salih et al., 2023). A study in Erbil included 289 patients and found deficiencies in 51.9% and insufficiencies in 27.6%. VDD was also most prevalent in females (55.5% vs 49.4%) and associated with both diabetes, obesity, heart disease, and COVID-19 (Ameen et al., 2023).

Merecidisnakan a survey in Duhok of 11,143 residents ebreveal di overall shortage ye nayto 44.9% yahindat dewan the ages 20-40 (46.23%). The females (43.03%) are more deficient than males (37, 8%). The deficiency in Zakho district was found to be 38.19%. (Mohammed et al., 2021). Overall VDD was relatively high (~39%) with significant differences between genders (females 45% vs. males 17%) in Basrah (Hadi et al. 20065). In addition, among menopausal women in Basrah, 83% were deficient (Khisho & Alfahad, 2025). In Mosul VDD was lower at 59.7% among preschoolchildren, yet a staggering 93% in patients with allergicrhinitis (Khisho & Alfahad, 2025).

4.2. Kirkuk Governorate

Kirkuk governorate is located in the north of Iraq, has a mixed population with Kurdish Arabs and Turkmen ethnic groups, and appropriate representation and study in the Vitamin D status scientific literature is new. The most locally relevant and pertinent data, collected in a 9-month cross-sectional registry of 388 consecutive orthopedic outpatients attending the Azadi Teaching Hospital (a teaching hospital located in Kirkuk city) between December 2023 and August 2024 has recently been published (Rashid et al., 2025). This study found a very high prevalence of vitamin D deficiency as characterized in this case by serum values below 12 ng/mL, which was determined in 241 subjects (62.1% of the sample). In addition, vitamin D insufficiency (serum concentration 12-20 ng/mL) occurred in 77 subjects, accounting for 19.9%, and sufficient vitamin D status was reported in only a minority of participants: only 66 subjects (17.0%). The study population was mostly female (69.6% women), and the clinical setting of orthopedic outpatient care, where

patients most commonly presented with arthritis, chronic fatigue, or other musculoskeletal complaints, likely represents an over-representation of the much higher clinical burden of VDD in women who seek this type of medical service. Increased age ($p < 0.001$), male sex ($p = 0.004$), obesity ($p = 0.003$) and presence of chronic disease comorbidities ($p < 0.001$) associated with various orthopedic clinical presentations were recorded as statistically significant correlations (Rashid et al., 2025). The study's authors highlighted that there was nothing previously conducted in relation to vitamin D solely with Kirkuk governorate in mind, and therefore their findings could have large public health significance for the area. Importantly, the 62.1% deficiency rate discovered in Kirkuk is broadly reflected by information out of adjacent northern Iraqi urban communities, with a 51.9% deficiency commonness unveiled in Erbil (Ameen et al., 2023) and a high number distinguished in Duhok (44.9% lack percent). Those findings agree with the observations of multi-regional study that proved vitamin D deficiency is an important public health problem in northern Iraq which has relevant higher risk and should be addressed (Mahmood et al., 2025; Rashid et al., 2025).

4.3. Local Cut-Off Debate

According to these strong findings, authors suggested that the global cut-off value for biochemical and functional vitamin D deficiency should not be applied in each populations including areas of particularly high prevalence of vitamin D deficiency such as Basrah and proposed that genetic adaptation mechanisms combined with a process of short- or long-term physiological acclimatization processes might have shifted the PTH inflection point causing an alteration in relation between vitamin D status and parathyroid hormone secretion. The results of this innovative and provocative research, which are highly novel and internationally generalizable in terms of clinical practice, public health screening programmers and pharmacoepidemiologic Al purposes, provides dramatic implications for Iraq: if vitamin D deficiency is indeed defined as lower than globally-accepted target population levels then interventions based on population-readiness data being benchmarked to global standards may misclassify significant proportions of the local population whilst failing to identify those at physiological risk at the lower tail end of the distribution.

4.4. Clinical Associations in Iraq

Vitamin D deficiency (VDD) among Iraqi population have been extensively studied, and wide associations with cardiovascular, endocrine, infectious diseases, autoimmunity and mental health may suggest a public health impact. Despite a major evolutionary role for vitamin D, in the specific diabetes mellitus domain where VDD has been particularly well documented with phenomenal prevalence rates being joyfully counted among 90% of pediatric patients with type 1 diabetes mellitus as well as 71% of adult populations plagued by type 2 diabetes mellitus from the Duhok region compared to stratifications recorded in controls (6%) and non-stratified controls (40.6%) (Khisho & Alfahad, 2025) Moreover, a recent population-based study reviewed all older adults with type 2 diabetes who had co existent VDD in Baghdad and showed that an astoundingly overwhelming group 95.8% of these patients were glycaemically uncontrolled indicating either a direct effect on glucose metabolism or common risk factors presence not yet fully recognized for Vitamin D insufficiency versus poor metabolic control (Khisho & Alfahad, 2025).

Musculoskeletal manifestations, usually fitting with clinical diagnoses of osteomalacia and secondary hyperparathyroidism, are often the most common presenting complaints in Iraqi patients with VDD as highlighted by the large orthopedic dataset from Kirkuk (Rashid et al., 2025). These musculoskeletal manifestations demonstrate the local and systemic severity of vitamin D deficiency in regards to bone health and calcium metabolism. Multiple respiratory system associations have also been described: of 90 patients with allergic rhinitis in Mosul, 93% were VDD (56% severely deficient); likewise, a cohort reported vitamin D deficiency evident in 44.3% of bilateral bronchial asthma from Baghdad; additionally, approximately 14% of children admitted with severe acute lower respiratory tract infections in Duhok showed VDD (suggesting a possibly role for vitamin D status and severity of respiratory disease morbidity) (Khisho & Alfahad, 2025).

Conclusion Data from the present study performed in several clinical contexts demonstrate the socio-economic magnitude of vitamin D deficiency in Iraq and its diverse effect on general health and healthy subgroups that require further exploration.

4.5. Awareness and Health System Perspective

Reference: Mohammed salih et al. also revealed a significant gap in health literacy for Vitamin D deficiency (VDD)that may worsen its clinical burden in Sulaymaniyah, Iraq. More than 90% of respondents were aware of vitamin D, but specific knowledge was lacking, with only 18.3% knowing the target serum for optimal health. Furthermore, Cohen et al. Of the 1467 respondents in one survey, 55% used supplements but 90% would self-medicate without consulting a practitioner suggesting widespread unsafe and inappropriate dosing.

Moreover, another study in Baghdad revealed 74.3% of the respondents showed knowledge score classified as satisfactory, however, something concerning is that a quarter (76%) of reproductive-age Iraqi women were deficient. In the same way, laboratory records in 10,823 subjects in Erbil revealed a 78% fee of VDD. previous studies have shown that awareness does not translate into adequately maintaining vitamin d levels. Limited access to supplements, restricted food fortification and some socio-economic or cultural factors also need addressing for sufficiency (Sulaiman et al., 2024).

To tackle these deficits, the authors called for an immediate public education effort on benefits of whole food local sources of vitamin D, food fortification and sand exposure. They also firmly recommend the establishment of regular risk assessment and screening for VDD in primary health care, which could lead to early detection and monitoring. Such timely preventive measures would avert effectively the heavy public health burden of untreated VDD throughout Iraq (Mohammed salih et al., 2023).

5. Immunological Consequences of Vitamin D Deficiency

For the most part, the overwhelming majority of modern scientific research has historically been limited to exploring the direct and well-characterized relationship between vitamin D deficiency and its immediate skeletal effects; nonetheless, a wealthier and more extensive literature base specifically related to populations within the Middle East indicates that the systemic effects of vitamin D insufficiency extend well beyond bone health itself with significant impact on multiple non-musculoskeletal physiological systems throughout the human body. Most importantly, there is now an abundance of evidence that this due-to-poor-nutrition presents with a significant reduction in immunity, actually being a severely deleterious functional impairment of the general immune response leading to increased susceptibility to a range of serious and long-lasting chronic diseases. The lack of sufficient vitamin D leads to significant, widespread immunological effects throughout nearly all aspects of the complex network responsible for the immune responses in humans and animals alike, both in terms of expression programming on innate (early) responding immune system components as well as finetuning capabilities between these early responders and specialized adaptive arms. These major molecular and cell biological changes then initiate an intricate chain reaction of downstream biozusbilder effects that ultimately reveal themselves in a remarkably wide-ranging clinical spectrum, modulating (i) the lifetime risk for developing sudden acute infectious diseases while at the same time aggravating (ii) the inexorable progression of chronic autoimmune diseases and highly complicated cardiometabolic disorders.

5.1. Mechanistic Link to Immunity

Hormonal vitamin D regulates immune pathways follow physiological homeostasis at the molecular level. Vitamin D deficiency (VDD), reduces the level of calcitriol which, in turn, strongly inhibits mRNA expression of first line antimicrobial peptides cathelicidin (CAMP) and β-defensin 2 (DEFB4) (Matsumoto et al., 2023; Alswailmi et al., 2021). As a result, this compromises the capacity of macrophages to phagocytose and eliminate intracellular pathogens.

Active vitamin D [$1,25(OH)_2D_3$] promote MAC phagocytosis, chemotaxis, and autophagy under normal circumstances to clear pathogens (Ghaseminejad-Raeini et al., 2023). These functions are dysregulated in VDD and result in profound natural immunity repression.

In adaptive immunity, VDD cannot suppress Th1 activity and Th17 differentiation, thus unleashing a pro-inflammatory milieu characterized by high level of IFN-γ, IL-17 and TNF-α. Along with this, there is a reduction of the anti-inflammatory IL-10 and regulatory T cells (Tregs). On the other hand, calcitriol administration decreased these pro-inflammatory cytokines and increased vitamin D receptor (VDR) expression in activated T lymphocytes (Peruzzu et al., 2022).

Calcitriol-VDR signaling also induces Foxp3 expression, which is essential for Treg maturation. VDD affects this pathway decreasing immunological tolerance, inducing abnormal autoimmune features (Ghaseminejad-Raeini et al., 2023). In addition, VDD induces dendritic cell hyperactivation that aggravates infection related inflammation. Conversely, and to little calcitriol also generates hyperactivity B cells and differentiate into plasma cells (Chen et al., 2016; Zeng et al., 2020), followed by an autoantibody pathogenic autoimmune (Alswailmi et al. 2021).

Across the globe, VDD is linked with a higher incidence of RTI and VRI. This seasonal winter decline in vitamin D corresponds directly with annual geographical trends of respiratory morbidities (Cui et al., 2023), highlighting the importance of vitamin D status for optimal host defense against respiratory pathogens.

5.2. Clinical and Epidemiological Associations in the Middle East

The MENA region presents itself as a good clue for the study of VDD-induced immunometabolic effects owing to high rates of VDD together with type 2 diabetes (T2D), cardiovascular diseases and autoimmune disorders in that area. VDD is associated with decreased insulin secretion, development of insulin resistance, and apoptosis of pancreatic β-cell. The prevalence of VDD reaches 70-90% in Gulf and Iraqi T2D cohorts and is both a risk modifier, as well as a consequence, of diabetes-related dysmetabolism (Khisho & Alfahad, 2025). Additionally, a meta-analysis reported that vitamin D supplementation significantly decreased serum insulin, fasting glucose and insulin resistance (HOMA-IR) in T2D patients with therapeutic potency (Wang, 2023).

VDD promotes renin-angiotensin-aldosterone system (RAAS) leading to hypertension and arterial stiffness [6]. Specific VDR gene polymorphisms (i.e., FokI, BsmI) affect the activity of RAS and the risk of hypertension (Voltan et al., 2023). Although observational studies provide evidence for a strong link between cardiovascular complications including heart failure and stroke with VDD, these are not confirmed by trials of supplementation likely due to nutrogenomic heterogeneity (Carlberg, 2023; Haider et al., 2023).

Concerning autoimmunity, VDR polymorphisms (ApaI, FokI TaqI) are associated with a higher risk for lupus and rheumatoid arthritis in populations (Consiglio et al., 2022.) More than 1,000 genes are regulated by VDR and immune cells express VDR and the local signaling-producing enzyme CYP27B1. Specifically, the VITAL trial reported a 22% reduction in new-onset autoimmune diseases with vitamin D supplementation (Cutolo, 2023).

Considering the high prevalence of VDD in MENA and expected variation between MENA and European populations for polymorphisms in the gene for vitamin D receptor (VDR), further studies are needed to explore interactions between low vitamin D status and genetics via VDR. As of now there is a very important lack from literature available on the genetics and environmental factors predisposing autoimmunity in this particular population.

5.3. Intervention and Nutrigenomic Findings

Randomized controlled trials testing vitamin D supplementation have yielded highly heterogeneous, often inconsistent findings in relation to distinct immune-related health outcomes. Not all these trials, however, especially those conducted with more rigorously controlled experimental designs, have recognized any clinically relevant or statistically significant effects; others find clearly statistically important specific immunologic benefits (e.g., perhaps better parameters of innate immune function) along with lesser extents of pro-inflammatory cytokine signaling and decreased infections following supplementation. A complicated phenomenon that new nutrigenomic research has begun to explain and help clarify in a more comprehensive manner is the observed inconsistency or variability of findings (Carlberg, 2023). Firstly, the categorization by or statistics for individuals into discrete microscopic units responders as a high versus intermediate (mid) or low responder to vitamin D_3 supplementation depending on their patterns of gene expression response characterizing what we have referred collectively to as vitamin D response index along with population-based dosing approaches at present time are in all likelihood ineffective for the majority of any given cohort regarding both sufficiency and/or that appropriate use clinically. Like as for Middle Easterners as a branch of unique evolutionary origin with Genome and/or alleles frequencies upsetting vitamin D metabolism (Carlberg, 2023). This enhanced understanding provides strong basis for the design and application of personalized vitamin D supplementation programs which are guided by comprehensive genetic assays in major VDR, GC and CYP2R1 genes. Although this is still out of the reach of routine clinical and perhaps even daily healthcare provision (in an economy such as Iraq, for example), it clearly also represents a major frontier in the future research and clinical evolution of precision nutrition towards personalized medicine.

6. Genetic Determinants of Vitamin D Deficiency in Middle Eastern Populations

Recent large genome wide studies conducted in the region very strongly suggest that genetic variation regarding vitamin D status may be an important contributor to our understanding of why deficiency remains so common and prevalent in some populations within the Middle East today. This has evolved from early candidate-gene hypotheses that focused on genes influencing the vitamin D metabolic pathway to the first genome-wide association study (GWAS) of this trait, specifically in an Arab population. This transformative development has completely altered and greatly improved our understanding of the genetic complexity underlying VDD in non-European populations, making intervention-specific opportunities possible for each unique genetic background.

6.1. GWAS in the Qatar Biobank

Hendi et al. METHODS 6,047 Qatar Biobank (QBB) participants were analyzed. They found that the GC gene, a strong candidate that encodes VDBP having an identified large locus at chromosome 4q12. Newly identified sentinel variant rs2298850 ($p = 1.71 \times 10^{-8}$) is absent from European studies. Genomewide association studies identified two additional independent GC SNPs (rs11723621, P = 4.7 × 10−17; rs4588 P = 2.5 × 10−18) in Hendi et al.) 2023). In a later UK Biobank-based meta-analysis (N = 363,228), two new variants close to CYP2R1 (rs67609747 and rs1945603). Heritability of serum 25(OH)D in the Qatari cohort was around 18% and matched estimates from Europe, establishing a strong genetic contribution to vitamin D levels in spite of clear environmental exposures (Hendi et al., 2023).

The study also showed that PRSs calculated from European populations had considerably less predictive value in the Qatari cohort (Pearson R=0.098, AUC=0.680) (Hendi et al., 2023). The differential genetic architecture contributed to less transferability, such as distinct alleles frequency and Middle East-specific variants. The European PRS continued to be linked to VDD risk in Qatar, but their low efficacy limits clinical application and strongly emphasizes the urgent need for population-specific genetic risk assessment tools in Middle East (Hendi et al., 2023).

Related 2021 rare-variant GWAS of 13,808 QBB individuals gleaned further details around Middle Eastern vitamin D genetics by leveraging extensive local biobanks. This discovered new loci for rare variants, including CD36 and SLC25A37 ($p = 5.15 \times 10^{-12}$). In particular, association of SLC25A37 with cancer susceptibility and vitamin D signaling pathways was shown by Hendi et al. (2025). Our findings identify lipid metabolism, mitochondrial transport mechanisms or ancestry-specific rare alleles as important genetic determinants of the VDD burden in this region.

6.2. Vitamin D Pathway Gene Polymorphisms

In addition to The VDR gene incorporates a wide variety of functionally relevant polymorphisms that exhibit a defined and essential role in the complex control of immunological responses. of these, the FokI polymorphism (rs2228570) located in exon 2 causes a three-amino-acid shorter receptor isoform known as F allele or simply designated as the form that has significantly higher transcriptional activity than longer form. On the other hand, direct functional analysis of BsmI polymorphism (or rs1544410) indicated that it was located in intron 8 and primarily influenced the stability of VDR transcript which affected receptor response to UVB-induced production of circulating 25-hydroxyvitamin D. Furthermore, the TaqI polymorphism (rs731236), which is located in exon 9, can change the methylation status of that region and thus affect expression patterns. Additionally, the ApaI polymorphism (rs7975232), also found in intron 8, influences susceptibility to systemic autoimmune diseases, yet further molecular mechanisms underlying this influence remain incompletely characterized and more studies are needed to evaluate them (Voltan et al.,2023; Consiglio et al., 2022). The large immunogenetic significance of VDR gene variation is vividly illustrated by demonstrating the association of rs7975232 with all three major autoimmune connective tissue diseases (systemic lupus erythematosus SLE, rheumatoid arthritis and primary Sjögren's syndrome) in a well characterized Italian patient cohort (Consiglio et al., 2022). By contrast, parallel associations in Arab populations have not been well described and remain a subject of active investigation. In the United Arab Emirates, especially, it has been associated with a predisposition of Emirati individuals to type 2 diabetes mellitus, and interactive effects involving rs731236 have also been noted that modulate disease progression and severity (results that are interestingly consistent with those reported recently in Iraq reporting high frequency clusters of VDD/T2DM co-prevalence) (Voltan et al., 2023).

6.3. Concept of Vitamin D Resistance

In the clinical and epidemiological milieu of a population who may experience low serum 25(OH)D chronically due to endemic deficiency attributable not to vitamin D availability but rather environmental or nutritional or lifestyle conditions but where, paradoxically, some individuals with biochemically-defined and measured vitamin D deficiency demonstrate more profound and attenuated PTH responses than others as inferred from the Basrah cut-off study (Alabbood & Alrubaye 2026), differential receptor sensitivity/desensitization/responsiveness has emerged as a conceptual model that could help explain this apparent elephant in the room notion borne of complex reality between vitamin D status vis-a-vis various clinically-relevant endpoints. This complexity also highlights the distinction between vitamin D deficiency, which can be regarded as the availability of its ligand 25(OH)D (or lack thereof), and vitamin D resistance (a circulating levels at which responsiveness is low level or signaling activity apparent sufficiency). The discovery of polymorphisms relevant as regulators on metabolism and/or VDR action (or lasting effects regarding clinical outcomes) would be the basis to appropriately management vitamin D supplementation policies, particularly when it comes to the above populations at higher genotypes frequencies of VDR gene.

7. Gaps in Research and Future Perspectives, Focusing on Iraq

Development: Despite the considerable and overwhelming evidence suggesting widespread of hypovitaminosis D in Iraqi communities, essential steps are needed to elucidate its bacteriological-genetic foundations as well as the immunobiological outcome delivered by hypovitaminosis D in Iraq. It is both remarkable and significant that there is a near-to-total absence from Iraq of the type of genomic data as presented here for the extensive richness and depth of the Qatari genetic dataset, despite its population size being approximately four folds larger than Qatar, and maintain a unique genetic admixture that has been established by continuous regional migration pressures through millennia. The lack of genetic and immunological research in this important population is obvious, as well as the clear need for those advanced studies due their high burden of vitamin D deficiency (VDD) in Iraq when approached from an absolute number perspective based on current estimates; additionally, VDD represents a major global health problem.

7.1. Limited Genetic Data from Iraq

To our knowledge, there is currently no any publicly-available GWAS or large-scale population genetic study of vitamin D levels in Iraq. Oldest research on Iraqi samples regarding polymorphisms in genes which are implicated to involved in vitamin D metabolism such as VDR, GC or CYP2R1 is limited due to the low number of candidate gene studies mostly performed on small clinical cohorts without appropriate sampling from the general population. Extrapolating the genetic risk architectures identified from European GWAS-a strategy that has already shown limitations in predicting polygenic risk scores (PRS) within Qatari populations as demonstrated by Hendi et al. (2023)-or interpreting conclusions based on data from Qatar to the Iraqi population-is methodologically unsound. This is probably because of the significantly different history of this population, the very peculiar to Iraq genetic structure between tribes and the expected population-specific allele frequency distributions in key genes within the vitamin D metabolic pathway. Thus, beginning a nationwide and systematic effort to create a unified cohort of Iraqi biobank linked to genetic, biomarker and clinical information would fundamentally revolutionize the ability of science and medicine to overcome this critical data gap.

7.2. Need for Integrated Gene-Environment Research

To measure the contrasting long-term influences of genetic determinants and environmental exposures, future researchers will have to abandon fragmented methodologies for integrative, multidimensional frameworks able to capture nonlinear interactions through time. In particular, we need research that is: F Mean serum 25-hydroxyvitamin D3 and parathyroid hormone (PTH) were quantified seasonally adjusted.

Key vitamin D-related SNPs across GC, CYP2R1, VDR and CYP27B1 loci. IFN-γ, IL-10, TH 17 and TNF-α measure immune markers, including discrete lymphocyte subtypes. Record phenotypic data of garments worn or layering individual styling behaviours. Incorporating regional geographical and social differences, a national multi-governorate analysis across Iraq. But the absence of data for Kirkuk would limit how widely applicable these lessons can be drawn across Iraq relative to past analyses (Rashid et al. 2025.) Nevertheless, the analysis contains some crucial evidence to assess inflexible vitamin D thresholds. More importantly, it elucidates whether the Basrah threshold laid down by Alabbood and Alrubaye (2026) applies across different areas or should be dismissed. Before any large-scale public health interventions of vitamin D can be recommended, this rigorous evaluative process is required.

7.3. Public Health and Policy Implications

Vitamin D deficiency (VDD) is a critical public health problem facing many regions worldwide including Iraq with high VDD rates. Some screening papers suggested targeted screening in high risk groups (women of reproductive age, elderly with chronic diseases and residents of high prevalence areas as Kirkuk and northern regions) to optimize the limited healthcare resources (Rashid et al., 2025; Mahmood et al., 2025). Moreover, effective campaigns on a large scale are essential to more efficiently correct behaviors by providing instruction of adequate sun exposure times and utilizations of food rich in high contents of vitamin D food sources and elucidate the limitations linked to exclusive plant-based diets (Mohammedsalih et al., 2023). A national fortification of staple food such as flour, oil and dairy is an effective and low-cost intervention of public health importance for the Iraqi background (Machuron et al., 2025).

In the long term, once genetic data from Iraq become available, it will be optimal to provide personalized supplementation targeting individual genetic risk profile (e.g. GC and CYP2R1) and environmental factors as the most efficient complementary measure towards VDD reduction (81), ultimately curbing its detrimental immunological (82-84) and cardiometabolic outcomes. It could utilize validated PRS tools specifically designed for Iraqis as unadjusted European PRS models have shown poor predictive accuracy in Middle Eastern populations (Hendi et al., 2023).

8. Conclusion

In the Middle east (Iraq being located herein), vitamin D deficiency (VDD) is a well-known widespread problem that effects immunity due to environmental, cultural and genetic reasons. Contrary to the abundant sunlight, the Eastern Mediterranean is presented with a high prevalence of VDD and has been associated to sun-restricting cultural patterns, sedentary lifestyle, low levels of dietary fortification, and genetic predisposition affecting vitamin D metabolism and receptor mechanisms. Vitamin D deficiency (VDD) is widespread in Iraq, ranging from 39%-45 % in Basrah; 84%-89% in Baghdad; and among children, 62.1% deficiency and 19.9% insufficiency from Kirkuk (Mahmood et al.,2025 Rashid et al.,2025 Khisho & Alfahad,2025). During our investigations in Basrah, we recommended a more locally-adapted cut off of 12.5 ng/mL that actually better represented the sedentarised chronically suboptimal vitamin D populations than standard international cut-offs (Alabbood & Alrubaye, 2026).

VDD reduces both innate and adaptive immunity by down-regulating the synthesis of antimicrobial peptides, inhibiting macrophage activity, skewing T-cells toward a pro-inflammatory phenotype, and impairing regulatory T cells. Thus, long-term VDD is a contributing factor behind MENA's sky-high morbidities from communicable, autoimmune, and cardiometabolic diseases (Alswailmi et al. (2023); Haider et al. (2023), 2021; Ghaseminejad-Raeini Due to over 1,000 genes that are regulated by the vitamin D receptor (VDR), these immune functions are mediated through the VDR. The VITAL trial reported a 22% reduction in autoimmune diseases with vitamin D supplementation, demonstrating its therapeutic potential (Cutolo, 2023). In addition, genetic studies demonstrate an array of variants within loci set for example GC, CYP2R1 and VDR where investigations reveal unique objects in Middle Easters cohorts as compared to European populations. The heritability of vitamin D traits in this population is ~18%, weakening the predictive power of European-based polygenic risk scores for the Middle East (Hendi et al., 2023; Rahman et al., 2023). This emphasizes the substantial individual variation in these levels, indicating that a universal population wide supplementation is insufficient.

Therapeutic interventions need to be tailored by individual genotypes and metabolic health (Carlberg 2023). There is an urgent need for integration of public health measures through targeted clinical screening, deployment of sufficient population-based education and fortification approaches in Iraq. Unfortunately, Iraq has no genomic infrastructure for sophisticated diagnostic and therapeutic tools to research vitamin D. In an effort to fill this gap, we aim to provide a genomics-driven translational platform. This infrastructure gap is a priority to protect the physiological health of populations as a public good.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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